

TABLE 1

**Genetic Epidemiology and Core Public Health Functions in the
Continuum from Genes to Public Health**

Step	Description of activities	Disease/gene examples
GENETIC TECHNOLOGY HUMAN GENOME PROJECT	Gene mapping and linkage studies in high risk families	50,000-100,000 genes such as BRCA1 in breast cancer
<div style="text-align: center;"> </div> <div style="text-align: center;"> </div> <div style="text-align: center;"> </div> <div style="text-align: center;">V</div>	GENETIC EPIDEMIOLOGY	
ASSESSMENT		ApoE E4 allele and Alzheimer's disease
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POLICY DEVELOPMENT	When and how genetic tests are to be applied in public health programs	Screening for various genes
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ASSURANCE	Development of public health genetic programs, evaluation of prevention effectiveness, quality assurance	Newborn screening for metabolic disorders; proficiency testing for newborn screening

TABLE 2

Genetic Epidemiology and Assessment of the Role of Genetic Factors in Disease

Aspects	Examples
<u>I. Population studies</u>	
A. Prevalence of susceptibility alleles in various populations	Studies of the frequency of BRCA1 mutations in different ethnic groups
B. Determinants of mutations in various populations	Studies of risk factors for chromosomal anomalies such as Down syndrome
C. Association between genetic traits and diseases	Studies of ApoE-E4 allele in Alzheimer's disease in the population
<u>II. Family studies</u>	
A. Familial aggregation of diseases	Recurrence risks of birth defects after an affected pregnancy
B. Causes of familial aggregation of disease	Studies of genetic and environmental factors in the recurrence of various diseases
C. Establishing genetic modes of inheritance	Segregation and linkage analysis in families

TABLE 3

Gene-Environment Interaction Analysis in a Case-Control Study

Exposure	Suscep- tibility genotype	Cases	Controls	Odds Ratio
(1=present, 0=absent)				
0	0	A_{00}	B_{00}	$OR_{00} = 1.0$
0	1	A_{01}	B_{01}	$OR_{01} = A_{01}B_{00} / A_{00}B_{01}$
1	0	A_{10}	B_{10}	$OR_{10} = A_{10}B_{00} / A_{00}B_{10}$
1	1	A_{11}	B_{11}	$OR_{11} = A_{11}B_{00} / A_{00}B_{11}$

Case-only odds ratio $OR_{ca} = A_{11}A_{00} / A_{10}A_{01} = (OR_{11} / OR_{10}OR_{01})OR_{co}$

Where $OR_{co} = B_{11}B_{00} / B_{10}B_{01}$ (control-only odds ratio)

TABLE 4

Case-Control Analysis of the Interaction Between Maternal Cigarette Smoking, Transforming Growth Factor Alpha Polymorphism, and the risk for cleft palate. Adapted from Hwang et al. (11)

Smoking	TaqI Polymorphism	Cases	Controls	Odds Ratio	95% C.I.
-	-	36	167	1.0	Referent
-	+	7	34	1.0	0.3-2.4
+	-	13	69	0.9	0.4-1.8
+	+	13	11	5.5	2.1-14.6

Crude odds ratios are presented.

Odds ratio based on a case-only study is 5.1 (95% C.I. 1.5-18.5)
 $(13 * 36) / (13 * 7)$

TABLE 5

Characteristics of Nontraditional Case-Only Studies

Feature	Case-Only	Case-Parental Control	Affected Relative-pair
Study Subjects	Cases	Cases and their parents	Second case in family, proband, and parents
'Controls'	None	Expected genotype distribution based on parental genotypes	Expected distribution of alleles with Mendelian transmission
Assessment	Departure from multiplicative relation between exposure and genotype	Association between genotype and disease Also departure from multipli- cative relation	Linkage between locus and disease Also departure from multipli- cative relation
Assumptions	Independence between genotype and exposure	Mendelian transmission	Mendelian transmission
Strengths & limitations	Simple. Cannot assess effects of expo- sure or genotype. Linkage dis- equilibrium	Requires one or both parents. Cannot assess exposure effects. Linkage disequilibrium	Need families with 2 or more cases. Cannot assess exposure Cannot assess specific

TABLE 6
Gene-Environment Interaction Analysis in the Context of a Case-Parental Control Study: Analysis of Nontransmitted Alleles

		Susceptibility genotype	
Exposure: Absent		Cases	
		Present	Absent
Parental non-transmitted alleles	Present	T_0	U_0
	Absent	V_0	W_0
Odds Ratio (among unexposed)		1	U_0/V_0
Exposure: Present		Cases	
		Present	Absent
Parental non-trans-	Present	T_1	U_1

mitted alleles

Absent

V_1

W_1

Odds

1

U_1/V_1

Ratio (among
exposed)

TABLE 7

Gene-Environment Interaction Analysis in the Context of an
Affected Sib-Pair Study

No. Alleles ibd with	Unexposed case	Exposed case	Expected	Odds Ratio (unexposed)	Odds Ratio (exposed)
0	A_{00}	A_{01}	0.25	1.0	1.0
1	A_{10}	A_{11}	0.50	$A_{10}/2A_{00}$	$A_{11}/2A_{01}$
2	A_{20}	A_{21}	0.25	A_{20}/A_{00}	A_{21}/A_{01}

TABLE 8

**Incorporating a Familial Analysis of Reconstructed Cohorts into a
Case-Control Study**

Disease in a Relative	Disease in Index Persons	
	Case	Control
Yes	A_1	A_0
No	B_1	B_0
Total	N_1	N_0

Total of case relatives is N_1 and control relatives N_0 .

Disease proportion in case relatives A_1/N_1

Disease proportion in control relatives A_0/N_0

Risk ratio $(A_1/N_1)/(A_0/N_0)$

TABLE 9

Linkage analysis in an Epidemiologic Study Design

Alleles ibd w probands	Cohort study		Case-control study		
	Disease Risk	Risk ratio	Recurrent cases	Controls	Odds ratio
0	R_0	1.0	A_0	B_0	1.0
1	R_1	RR_1	A_1	B_1	A_1B_0/A_0B_1
2	R_2	RR_2	A_2	B_2	A_2B_0/A_0B_2